DISSERTATION

ON

ROLE OF NEO-ADJUVANT CHEMOTHERAPY IN DOWNSTAGING CARCINOMA BREAST.

Dissertation submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

In partial fulfilment of the regulations

for the award of the degree of

M.S. - GENERAL SURGERY- BRANCH – I

THANJAVUR MEDICAL COLLEGE,

THANJAVUR - 613 004.

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI - 600 032.

APRIL - 2013

CERTIFICATE

This is to certify that this dissertation entitled "**ROLE OF NEO-ADJUVANT CHEMOTHERAPY IN DOWNSTAGING CARCINOMA BREAST.**" is the bonafide original work of **Dr.MUTHUVINAYAGAM A** in partial fulfilment of the requirements for M.S Branch -I (General Surgery) Examination of the Tamilnadu Dr. M.G.R. Medical University to be held in APRIL - 2013. The period of study was from August - 2011 to November - 2012.

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DECLARATION

I, **Dr.MUTHVINAYAGAM A**, solemnly declare that the dissertation titled **"ROLE OF NEO-ADJUVANT CHEMOTHERAPY IN DOWNSTAGING CARCINOMA BREAST."** is a bonafide workdone by me at Thanjavur Medical College, Thanjavur during August 2011 to November 2012 under the guidance and supervision of **Prof.Dr.V.BALAKRISHNAN, M.S.,** Professor and Head of the department,department of general surgery, Thanjavur Medical College, Thanjavur.

This dissertation is submitted to Tamilnadu Dr. M.G.R Medical University towards partial fulfilment of requirement for the award of **M.S. degree (Branch -I) in General Surgery**.

Place: Thanjavur.

Date: - 12 - 2012. **(Dr.MUTHUVINAYAGAM A)**

ACKNOWLEDGEMENT

I gratefully acknowledge and my sincere thanks to **Prof.Dr.C.GUNASEKARAN, M.D., DCH.,** Dean, I/C Thanjavur Medical College, Thanjavur, for allowing me to do this dissertation and utilize the institutional facilities.

I am extremely grateful to **Prof.Dr.V.BALAKRISHNAN, M.S.,** Professor and Head of the Department, Department of General Surgery, Thanjavur Medical College, for his full-fledged support throughout my study and valuable suggestions and guidance during my study and my post graduate period.

I profoundly thank my respected Professors **Prof.Dr.Maragathamani Ilangovan,M.S., Prof.Dr.Elangovan,M.S., Prof.Dr.D.Nagarajan,M.S., Prof. Dr. Rajagopal, M.S., Prof.Dr.Shanthini, M.S., Prof.Dr.Karunakaran,M.S., Prof.Dr.Padmanabhan,M.S., Mch**., Department of Surgical Gastroenterology, **Prof.Dr.A.Rathinavel,M.S.,Mch.,** Department of Cardiothoracic Surgery, and **Dr.Eganathan,M.S.,** (Registrar), for their advice, guidance and valuable criticism which enabled me to do this work effectively.

I would like to express my gratitude to **Prof.Dr.Murugavel, M.D.,** Professor and Head, Department of radiotherapy for his immense help in the study which enabled me to complete this work.

My sincere thanks to assistant professors **Dr.A.Michael,M.S.,Mch., Dr.S.Jegatheesan,M.S., Dr.Mohammedzaheer.M.S.,Mch., Dr.S.Marimuthu,M.S.,Mch., Dr.S.Muthuraman,M.S., Dr.V.Marimuthu,M.S., Dr.S.R.Padmanabhan,M.S.,** for their motivation, encouragement and support.

I would like to thank Assistant Professors of other unit, my colleagues and friends who have been a constant source of encouragement.

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INTRODUCTION

LABC refers to a diverse and heterogenous group of people with breast cancer which represents one of the commonest malignancy of female population in our region.

Patients with this cancer include those with operability at presentation, and inoperability at presentation. Which include stage IIb, IIIa and IIIb. This study also included supra clavicular node in the locally advanced breast cancers.[1]

Over the past few decades, the management of the LABC has considerably evolved from radical mastectomy alone to multidisciplinary modalities involving surgery, chemotherapy and radiotherapy(RT) . With the advent of Neo adjuvant Chemotherapy many of the previously inoperable tumours have become amenable to surgery.

Preoperative administration of hormonal therapy or systemic chemotherapy can result in considerable fall in tumour size in 50% to 80% of the LABC. Patients living with LABC have poor prognosis when treated

with surgery or RT. They include Stage IIb, III A and III B according to the American Joint Committee on Cancer (AJCC).

As a consequence of these poor outcome neo adjuvant chemotherapy has been introduced. This approach is designed to render patients operable, and to eradicate micro metastases at an early stage,. In General only 3-4 cycles of conventional doses of Neo adjuvant Chemotherapy given prior to surgery. Hekmen et al showed that clinical response rate to Neo adjuvant chemotherapy varies between 80% and 90% .

The Neo adjuvant chemotherapy (NACT) enhanced the quality of life of LABC patients. NACT reduced the morbidity and improved the overall survival rate and disease free interval.

AIM AND OBJECTIVES

1. To determine the role and outcome of Neo adjuvant chemotherapy administered in Locally Advanced Breast Cancer (LABC).

2. To determine and study what extend the inoperable LABC become amenable to surgery.

3. To evaluate the role of NACT in improving the quality of Life, morbidity in LABC patients.

LIMIATATIONS OF THE STUDY

1. This study is limited with only one Imaging modality(CT Scan) to predict the clinical and pathological response of tumour.

2. Unresolved issues are there like (a) Selection of Patients, (b) Tumour factors, (c) Clinical factors, and (d) Regional lymph nodes.

3. This study also used fixed cycles of NACT to get optimum response to convert inoperable tumor to an operable one. Instead of 4-6 cycles used in the international studies we used only 3 cycles of chemotherapy.

4. Some of the patients didn't turn up for review and follow up.

HISTORICAL PERSPECTIVES

Edwin Smith, surgical papyrus 3000-2500 BC was the first document that referred to carcinoma of Breast. The lesion was in a man but the description encompassed most of the features of Breast cancer. Direct reference to treatment of breast cancer is conspicuously absent in the corpus Hippocraticous.

Celsus documented the value of surgical management for early breast cancer(EBC) in his early Roman writings of the first century A.D. In the 2nd century Galens system concluded that extension of local outbreak could not cure the systemic imbalance.

Beginning with Morgagni's systematic approach modalities that varied from those espoused by Galen were acceptable. In 19th century , Moore, a consultant worked in Middlesex Hospital placed in London enumerate wide removal of carcinoma breast. Bank supported Moore's concepts. in 1894, Halsted & Meyer simultaneously documented their surgeries for management of cancer of the Breast, the radical mastectomy. Patey of

Middlesex Hospital, London presented modified radical mastectomy in 1930.[3]

Samuel D Gross (b.1805) was designated as "The Greatest American surgeon of his time". His approach to carcinoma breast was more conservative, using a small elliptical incision he attempted to save enough skin for easy approximation of the edges of the wound.

Paget (B.1814) described cancer of nipple accompanied by the eczematous change and cancer of lactiferous ducts.

Richard Von Volkmann (b.1830) removed the entire breast no matter how small the primary tumor, as well as the pectoral fascia with an occasional thick layer of the underlying muscle and the axillary nodes.

Ernst Kuster (b.1839) of Berlin recommended that the axillary fat be removed along with axillary nodes.

William Welch (b.1850) a pathologist at Johns Hopkins was the first to use frozen section in the diagnosis of breast lesion.

William Halstead (b.1850) recommended "The suspected tissue to be removed in one piece" he advocated such wide removal of skin that a graft would be required and recommended that pectoralis major be part of the enbloc specimen regardless of the size of the tumor. This procedure

"Halstead's radical mastectomy" was unchallenged for 70 years until the advent of breast conservation methods.

Wille Meyer (b.1854) described a similar technique only 10 days after Halstead's published paper; he advocated removal of pectoralis minor in addition to pectoralis major.

In 1937 Geoffry Keynes demonstrated that less radical surgery was needed in breast cancer with radiation giving good results. In 1948 two reports appeared that were destined to change the management of breast cancer. The first was the concept of modified radical mastectomy by D.Patey and W.Dyson. The second was treatment with simple mastectomy and radiotherapy by R We Whirter.

In 1977 William Handley (b.1872) directed attention of the frequency of internal mammary node involvement. He reported the removal of internal mammary nodes as an extension of radical mastectomy.

In the late years of 20th century, Donold Morton at the John Wayne cancer centre in Santa Monica, CA developed the sentinel lymph node biopsy technique.

Two months after the invention of X-ray, Emil Grubbe (b.1875) irradiated a patient with breast cancer.

In 1889 Albert Schinzinger (b.1927) proposed oophorectomy before mastectomy to produce early aging in menstruating woman.

In 1953 Charles Huggins advocated oophorectomy and adrenalectomy to remove the major source of oestrogen in the body.

CHANGING STRATEGIES

In the last few decades treatment strategies for breast cancer have undergone significant changes. The main shift is in the concept of "Maximum tolerated treatment to the minimum effective treatment."

The Halstedian concept of radical mastectomy dominated the treatment philosophy until 4 decades ago. Breast cancer was considered as a local disease. In the 1960's based on a series of randomized trials, Bernard Fisher proposed that Early Breast cancer is a systemic disease involving a complex spectrum of host tumor interactions. Hence loco regional treatment for breast cancer is unlikely to have an effect on survival.[6]

Based on this concept, the efficacy of adjuvant chemotherapy was proved by studies done by Bonadone et al. and National Surgical adjuvant breast and Bowel Project (NSABP) 1971.[7,8]

NEOADJUVANT CHEMOTHERAPY

Neo Adjuvant Chemotherapy was first introduced in 1973 in the Milan cancer institute aimed at achieving prompt tumor shrinkage.[9] NSABP – 18 in 1988 clearly established the efficiency of Neo Adjuvant Chemotherapy in tumor shrinkage and thereby avoiding mutilating surgeries.[10]

Preoperative administration of hormonal therapy or systemic chemotherapy can result in a considerable decline in tumor size in 50% to 80% of patients with LABC. This neo adjuvant therapy can convert inoperable tumors to operable ones. Neo adjuvant chemotherapy can change tumors that would need for mastectomy to eligibility for lumpectomy, and can reduce bigger tumors to allow a more cosmetic lumpectomy. This study allows to evaluate tumor biology through continuous analysis of tumor tissue before, during, and after treatment. This is used to study the mechanism of action and potency of systemic chemotherapeutic agents.

Many randomized, prospective trials analysed the effectiveness of hormonal therapy and chemotherapy given preoperatively (neo adjuvant) versus after (adjuvant) definitive surgery. All these studies documented increased rates of breast conservation with the use of chemotherapy

preoperatively. The National Surgical adjuvant breast and Bowel Project B-18 trials included 1522 patients and found no survival advantage in patients who received chemotherapy preoperatively with cyclophosphamide and doxorubicin chemotherapy versus the same regimen administered randomized postoperatively. In women who received neoadjuvant chemotherapy had higher chance for breast conservation surgery, and recurrence in breast after neoadjuvant therapy was not significantly different from that in women who completed lumpectomy and postoperative chemotherapy. Response to neoadjuvant chemotherapy was found to have direct relation with prognosis. At 9 years of follow up the disease free survival rate in patients achieving a complete pathologic response in the preoperative arm (no evidence of tumor at surgery) was 75% in contrast to 58% in patients who had any residual invasive disease left after chemotherapy.

In practice, the neo adjuvant chemotherapy is used routinely for patients with inoperable LABC. This includes inflammatory breast cancer, huge, fixed or erosive inoperable lesions, and advanced, fixed node with arm edema. These patients will then undergo surgical procedure, radiation therapy, and additional systemic chemotherapy.[2]

ANATOMY

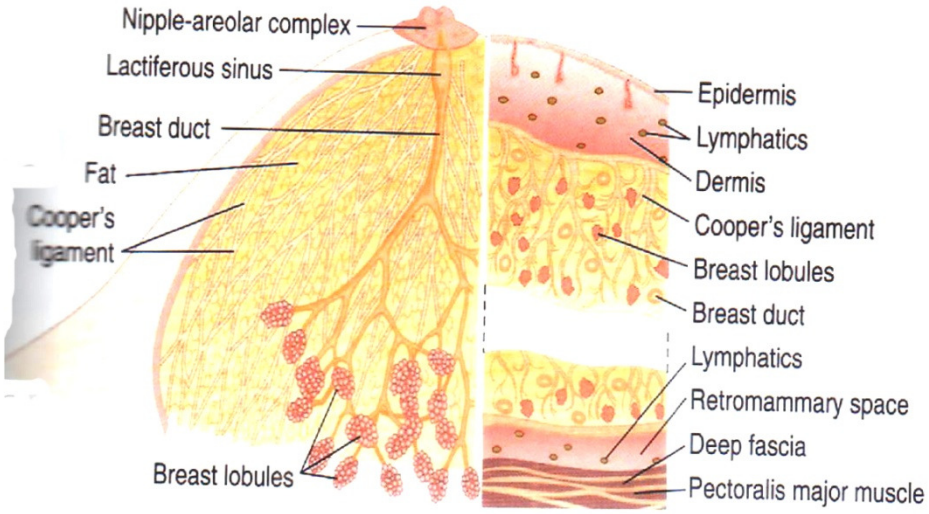
The paired mammary gland develops from remnant milk ridge in the pectoral region. Breast is a highly modified sudoriferous gland that develops as ingrowth from ectoderm and form Acini & Duct. The supporting vascularised connective tissue takes derivation from the mesenchyme. By birth lactiferous duct open into mammary pit.

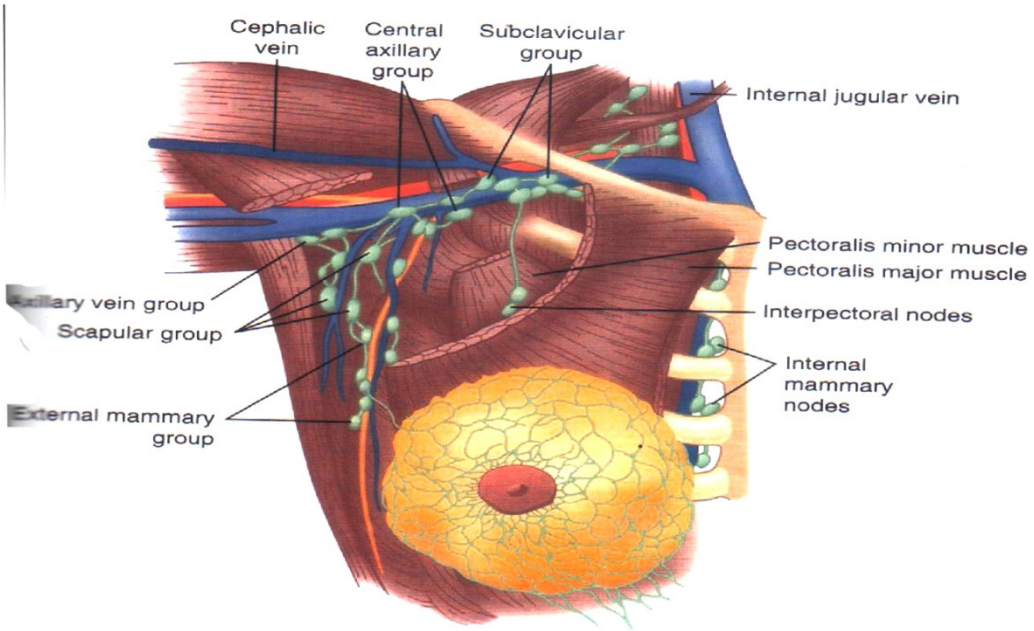
The mature breast is overlying the second to Sixth rib and having medial boundary at lateral border of the sternum and lateral boundary at anterior axillary line.

Lobule is the basic structural unit of mammary gland. The size and number of the lobule differ enormously. They are numerous in young women. From 10 to 100 lobules empty via ductules into Lactiferous duct.

Cooper's ligaments are hollow conical projections of fibrous tissue filled with mammary tissue and the apices of the cones are firmly attached to the superficial fascia and skin.[2]

ANATOMY


Nipple-areolar complex
Lactiferous sinus
Breast duct
Fat
Cooper's ligament
Breast lobules
Epidermis
Lymphatics
Dermis
Cooper's ligament
Breast lobules
Breast duct
Lymphatics
Retromammary space
Deep fascia
Pectoralis major muscle


Cephalic vein
Central axillary group
Subclavicular group
Internal jugular vein
Pectoralis minor muscle
Pectoralis major muscle
Interpectoral nodes
Internal mammary nodes
Scapular group
External mammary group

BREAST DEVELOPMENT AND PHYSIOLOGY

Before puberty, the mammary gland is mainly formed by dense fibrous tissue and scattered ducts, lined with epithelium. Pituitary gonodotropins raise serum estrodial concentrations during puberty. In the breast there is increased deposition of fat forming new ducts which is done by branching and elongation of lobular units. This is the first appearance of lobular units. This process of cell division and cell growth depends upon the estrogen, progesterone and adrenal Hormones. Post pubertal breast contains fat, lactiferous duct, stroma and lobular units. During the period of menstrual cycle the breast epithelium and lobular stroma, undergo cyclic stimulation. The dominant process is alteration of morphology and hypertrophy.[2]

INVESTIGATIONS

DIAGNOSTIC MAMMOGRAPHY

Also called consultative or problem solving. It is indicated when there are clinical findings such as palpable lump or abnormal results on a screening examination

Capabilities:

-Can define the nature of many breast abnormalities.

- Can identify unexpected malignancy.
- Can identify multi focal disease. Indications of Diagnostic mammography;
- Over 30 years
- With/without lump before performing biopsy.
- To Detect unexpected lesions of ipsilateral/contralateral breast.
- To Identify the intraductal component of a palpable invasive carcinoma.
- To detect carcinoma in contra lateral breast after mastectomy.

- After surgery before radiotherapy to document all the calcification were removed
- At 6 months interval for 2 years after lumpectomy in later years.

Normal findings

1) Four categories
    1) Breast entirely fat.
    2) Scattered fibro glandular densities.
    3) Breast tissue is heterogenetically dense.
    4) Extremely dense.

Abnormal findings

1.Masses and calcifications are the most common abnormality encountered on mammograms and radiographic features of these abnormalities are important clues to their etiology. In standard report these masses and microcalcifications indicate likelihood of malignancy, other findings include finding of new evolving lesions.

- Bilateral asymmetrical distribution of fibroglandular tissue.
- Architectural distortion.
- Nipple retraction.
- Axillary LN enlargement.

DIGITAL MAMMOGRAPHY

- This type records the radiography image electronically in a digital format rather than a film.
- It is left in computer and displayed on fluorescent monitor.

ULTRASOUND

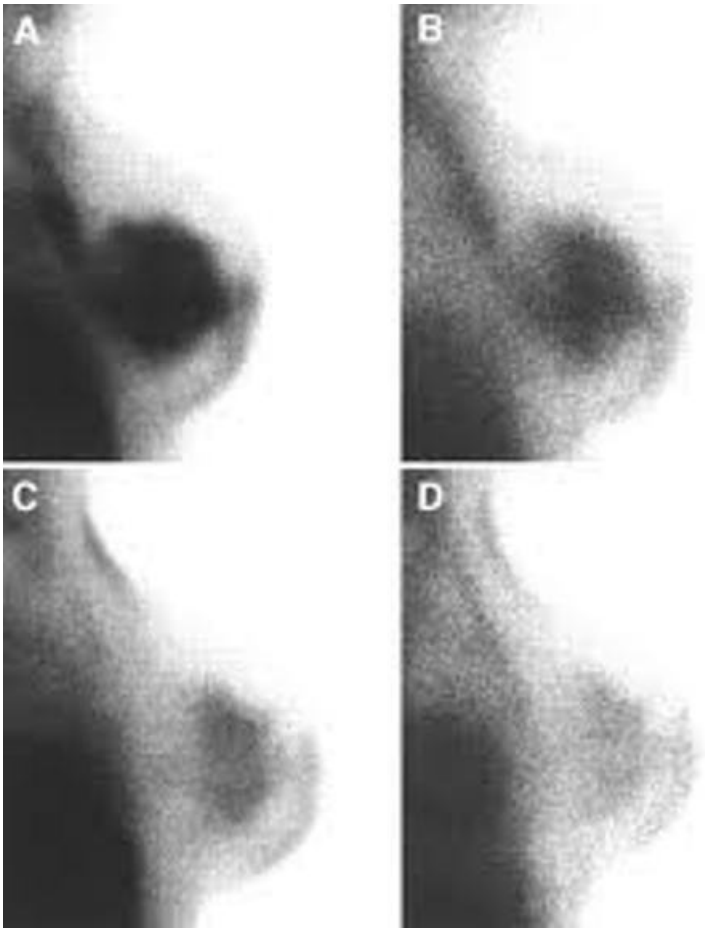
5) Useful in young women with dense breast tissue.

- Distinguish cysts from solid lesion.
- Used to localise impalpable areas of breast pathology.

6) Although USG is not efficacious as a screening modality, combined mammography and USG pick up more cancers than mammography alone.

COMPUTERISED TOMOGRAPHY

7) These play a major role in evaluating the axilla, medistinum and supraclavicular areas for adenopathy and may aid in clinical staging of malignant processes. Apart from this CT have no role in carcinoma breast management.



Mammogram ,before and after NACT

MAGNETIC RESONANCE IMAGING

MRI is of increasing interest in number of setting.

- It can be useful to distinguish scar from recurrence in women who have previous conservation for cancer (although it is not accurate within 9 months of radiotherapy because of abnormal enhancement).
- It is best imaging modality for the breast of women with implants.
- It is proven to be useful as a screening tool for high risk women (because of family history).
- It is less useful than ultrasound in the management axilla both in primary breast disease and recurrent disease.

THERMOGRAPHY

8) The heat emission from the breast surface is measured as infra-red radiation and then recorded. It is then displayed on a photographic plate/cathode

9) ray tube. It is based on the metabolism and vascularity of the breast tissue and is increased in infection and some malignancy.

INVASIVE TESTS

ASPIRATION CYTOLOGY

10) Involves use of a fine needle with a syringe to aspirate cells from a suspicious area, smearing them on a glass slide fixing them immediately to prevent air drying and then staging for cytology. The technique of aspiration cytology evolved from pretty easy aspiration from any needle to an elaborate system following a set of rigid rules. The purpose of these was to optimise the yield and making the interpretation easier and more reliable.

11) Instruments used are disposable plastic needles of varying length and of 22-26 gauge are used. Plastic syringes are used to create vacuum, the syringe can be attached to CAMEO syringe holder so as to perform single hand aspiration, and the advantage of this is that the other hand is used for fixation of the target.

Procedure

12) The lump is immobilized and if possible the skin over the lesion is stretched and cleaned with spirit, so that the needle reaches the target easily. The instrument is introduced into the lesion, then vacuum is created by about 2-3 ml, and the needle is moved back and forth 5-6 times. By this time tissue is

seen at the hub of the needle, if not seen then needle is withdrawn from the target till the subcutaneous tissue and redirected in other direction to repeat the same procedure.

13) Then the syringe is withdrawn filled with air and needle is brought in contact with the slide and one drop of tissue is deposited on one, tissue is spread with cover slip or a haematological smear is prepared if blood or aspirate is more.

14) Following the air dried preparation slide is stained with wrights/wrights Giemsa/May Grunnwald Giemsa. If not air-dried it is immediately fixed with 95% alcohol and staining is done with H&E stain/with pap stain.

15) Combination of physical examination, mammography and FNAC will produce a diagnostic accuracy approaching 100%.

16) FNAC is done in palpable mass, mass on mammogram. Sensitivity of the test is approximately 80%, false negative varies b/w 2-10%.25

17) Axillary US – FNAC reliably detect the node metastasis arising from both primary invasive ductal and lobular tumours.

Advantages

- Less expensive
- Less invasive

Complications of FNAC

- Growing out of tumor along needle tract, which is less in case of calibre < 20 gauze.
- Acute mastitis
- Pneumothorax
- Haematomas
- Interval of weeks required b/w FNAC and mammography as they form hematomas and result in false positive mammographic studies.

CORE NEEDLE DIRECTED BIOPSY

- Large bore needles are often used
- More invasive
- Better accuracy
- Can perform receptor determinations
- Can be done stereotactically
- USG-guided core biopsy used for preoperative axillary lymph node staging

CHEMOTHERAPY DRUGS

The most commonly used drugs in the chemotherapy of carcinoma breast are.

- Cyclophosphamide
- Methotrexate
- 5 Fluorouracil (5-FU)
- Doxorubicin
- Taxanes
    - Paclitaxel
    - Docetaxel

Cyclophosphamide

This alkylating agents have cytotoxic and radiomimetic actions. Act on dividing as well as resting cells. Cyclophosphamide has prominent immunosuppressant property.

Dosage: 2-3 mg/kg per day.Toxicity: Hemorrhagic cystitis.

Methotrexate

It is one of the highly efficacious anticancer drug. It inhibits dihydrofolate reductase(DHFR) blocking the alteration of dihydrofolic acid to tetrahydrofolic acid. Methotrexate acts via cell cycle – kills cells in S

phase.Methotrexate inhibits deoxyribo nucleic acid synthesis. Methotrexate also affects ribo nucleic acid and protein formation.

Toxicity –suppression of Bone marrow.

Fluorouracil (5-FU)

Fluorouracil (5-FU) is converted to the corresponding nucleotide 5-fluoro 2-deoxyuridine monophosphate.This component acts by inhibiting thymidylate synthetase and inhibits the change of deoxyuridilic acid to deoxythymidylic acid. It affects even when the cell is in the resting stage though rapidly multiplying ones are more susceptible.

Toxicity : Bone Marrow and G.I.T.intolerance.

Dosage : 12 mg/kg per day

Doxorubicin

This is obtained from microorganisms which have prominent antitumour activity. Practically all of them collect between DNA strands and interfere with its template function. It has mutagenic and carcinogenic properties. Maximum action occurs in S phase.

Toxicity : Cardiotoxicity, Marrow depression, alopecia, stomatitis and vomiting.

Taxanes

Docetaxel

It enhances polymerization of tubulin, a mechanism opposite to that of vinca alkaloids.

Toxicity : Neutropenia

Neuropathy

Hypotension

Arrhythmias

PATHOLOGY

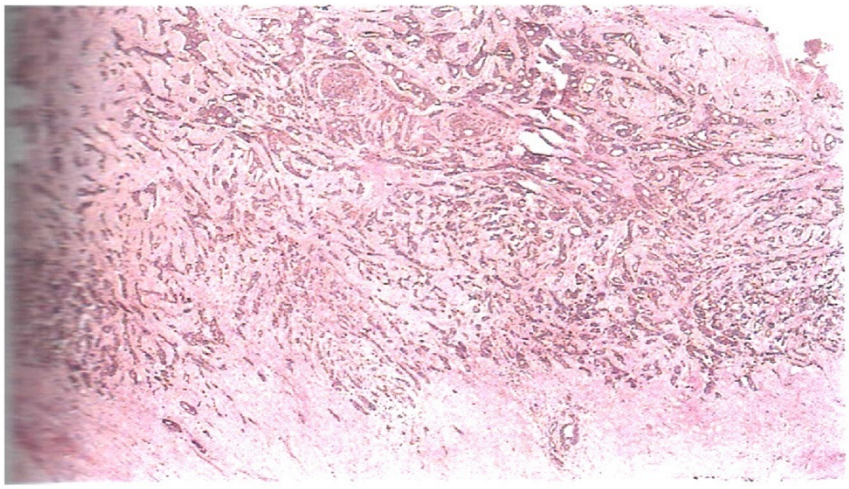
Breast cancer originates from the epithelium present in the terminal duct lobular unit of the mammary tissue. Those remaining within the basement membrane are classified as “in Situ” and have characteristic patterns as do invasive cancers which disseminate beyond the basement members.

Invasive cancers are now classified as

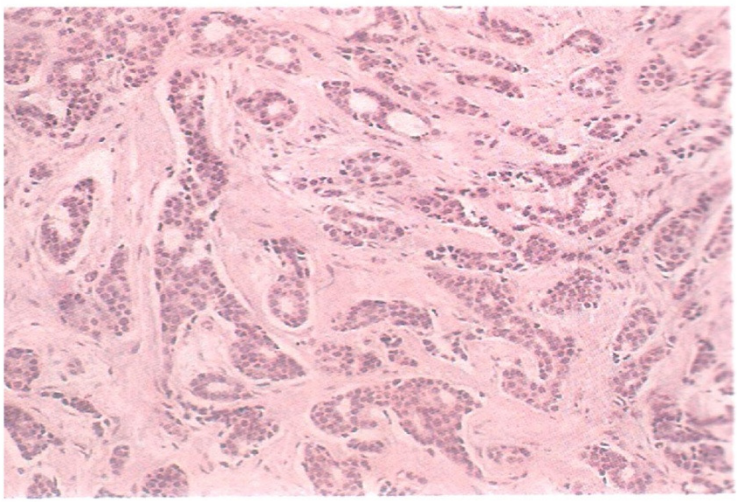
No special types (N.S.T. not otherwise specified) or special types.

- Lobular
- Tubular
- Medullary
- Mucoid
- Papillary

Which may have characteristic histopathological features and some of which may have a better prognosis. For cancer of NST, prognosis is related to tumor grade I, II and III based on gland formation, nuclear pleomorphism as originally described by Scarff, Bloom, P.Richardson.



INFILTRATING DUCT CARCINOMA, WELL DIFFERENTICIATED



INFILTRATING DUCT CARCINOMA (LOW POWER VIEW). NOTE TUMOR CELLS IN CORDS AND TUBULES INFILTRATING STROMA

Among invasive cancers 80% is NST, 10%is Lobular and the remaining 10% constitutes tubular, medullary, mucoid, papillary or other even rare types. “Lymphatic or vascular invasion on histological assessment is also a marker for both local and systemic recurrence.” Patients with perineural invasion or extensive (>25%) in situ cancer within the tumor mass are more likely to develop local recurrence.

Metastatic spread from breast carcinoma is via lymphatic channel to regional lymph nodes. Lymphatic and vascular invasion in the breast tissue is suggestive of the propensity of the cancer to spread to distant metastatic sites.

RISK FACTORS FOR BREAST CANCER

Factors important in populations,

- Age at menarche(onset of menstrual cycle) and menopause
- Parity(no of births)
- Age at first birth
- Breast feeding
- hormonal medications
- Alcohol consumption

FACTORS IMPORTANT IN INDIVIDUAL PATIENTS

- Gender
- Age
- Family History
- H/o Previous Breast Cancer

HISTOLOGICAL RISK FACTORS

- Proliferative breast disease
- Atypical ductal Hyperplasia
- Atypical Lobular Hyperplasia
- Lobular carcinoma in Situ.

GENETIC RISK FACTORS

5 to 10% of carcinoma breast are due to inheritance of germline mutations, which mainly occurs in BRCA 1 and BRCA 2. Carcinoma due to mutation of thse are autosomal dominant disorder with variable degree of penetrance. BRCA 1 is situated on chromosome 17q. BRCA 1 and BRCA 2 act as tumor suppressor genes. For each gene, loss of both alleles is

necessary for the initiation of tumour. BRCA -1 associated carcinoma breast are histologically IDC (invasive ductal carcinomas). These are poorly differentiated tumours and the hormone receptor status for these tumours are usually negative. Tumours due to BRCA -1 mutation have some unique clinical features.These tumours have early age of onset when compared with sporadic cases; there is higher chance of bilateral breast cancer. The other cancers associated with BRCA-1 mutation are ovarian tumour ,colonic malignancy and prostatic tumours.

BRCA -2 is located on chromosome 13q. Its associated carcinoma breast is IDC. This tumour histology belongs to well differentiated which also expresses more hormone receptors than BRCA-1 associated tumours. Breast tumour associated with BRCA -2 mutation has the characteristic feature of late onset. It has high chance of bilateral breast cancer. The associated cancers are from ovary, prostate ,colon, , pancreas, GB, bile duct, and stomach malignancy along with melanoma sometimes.

CLASSIFICATION OF PRIMARY CARCINOMA BREAST

Non Invasive Epithelial Cancers

- Lobular Carcinoma in Situ(LCIS)
- Ductal carcinoma in Situ(DCIS)

Invasive Epithelial Cancers

- Invasive ductal carcinoma(IDC) (10-15%)
- Mucinous tumours (2-3%)
- Medullary tumours (5%)
- Adenoid cystic tumours
- Metaplastic carcinoma (1-2%)
- Invasive Cribriform carcinoma (1-3%)
- Invasive papillary carcinoma (1-2%)

MIXED CONNECTIVE EPITHELIAL TUMORS

- Phyllodes tumor
- Carcinoma
- Angio sarcoma

STAGING OF BREAST CANCER

Breast cancer stage is determined by the results of surgical resection and imaging studies. The classification of Carcinoma breast is done with the TNM classification system, which concerns different patterns of breast, nodal, and distant tumor stages for prognostic purpose. The American Joint Committee on Cancer (AJCC) is widely used, which is on the basis of primary tumor (T), lymph node status (N), distant metastases if any (M), It is regularly updated to indicate current understanding of disease course. The most recent updates have incorporated sentinel node biopsy and include classification of the size of metastatic deposits in sentinel nodes, as well as the number and location of regional node metastases. The following table presents the TNM working guide.

AMERCAN JOINT COMMITTEE ON CANCER STAGING SYSTEM FOR BREAST CANCER, 2002

(p) T (Primary Tumor)

Tis	Carcinoma in situ (lobular or ductal)
T1	Tumor < 2cm.
T1a	Tumor > 0.1cm, < 0.5 cm.
T1b	Tumor > 0.5 cm, < 1cm
T1c	Tumor 1cm, < 2cm.
T2	Tumor > 2cm, < 5cm.
T3	Tumor >5cm
T4	Tumor any size which involves chest wall or skin
T4a	Tumor extending to the chest wall (excluding the pectroalis)
T4b	Tumor involving the skin
T4c	T4a and T4b
T4d	Inflammatory Ca

(p) N (Nodes)

N0	No regional node involvement, no special studies
N0 (i^-)	No regional node involvement, negative IHC
N0 (i^+)	Node(s) with isolated tumor spanning < 0.2mm.
N0 (mol-)	Negetive node(s) histologically, negative PCR
N0 (mol+)	Negetive node(s) histologically, positive PCR
N1	Metastasis involving 1-3 axillary nodes and/or int. mammary positive by biopsy.

N1 (mic)	Micrometastasis (>0.2mm, none >2.0mm)
N1a	Metastasis involving 1-3 axillary nodes
N1b	Metastasis in internal mammary node by sentinel biopsy
N1c	Metastasis involving 1-3 axillary nodes and internal mammary by biopsy.
N2	Metastasis to 4-9 axillary nodes or internal mammary clinically positive, without axillary metastasis.
N2a	Matastasis to 4-9 axillary nodes, atleast 1>2.0mm
N2b	Internal mammary clinically apparent, negative axillary

Nodes.

N3	Metastasis to > 10 axillary nodes or combination of axillary and int. mammary metastasis.
N3a	> 10 axillary nodes (>2.0 mm), or infraclavicular nodes.
N3b	Positive int. mammary clinically nodes with internal mammary positive by biopsy.
N3c	Metastasis to ipsilateral supraclavicular nodes.

M (Metastasis)

M0	No distant metastasis
M1	Distant metastasis

AMERICAN JOINT COMMITTEE ON CANCER STAGE GROUPING

STAGE	TNM	5-YEAR SURVIVAL RATE(%)
0	Tis, N0, M0	100
II	T1, N0, M0	100
IIA	T4, N1, M0 T1, N1, M0 T2, N0, M0	92
IIB	T2, N1, M0 T3, N0, M0	81
IIIA	T0, N2, M0 T1, N2, M0 T2, N2, M0 T3, N1, M0 T3, N2, M0	67
IIIB	T4, N0, M0 T4, N1, M0 T4, N2, M0	54
IIIC	Any T, N3,M0	20
IV	Any T, any N, M1	1

REVIEW OF LITERATURE

Neo Adjuvant Chemotherapy was first introduced in 1973 in the Milan cancer institute aimed at achieving prompt tumor shrinkage. NSABP – 18 in 1988 clearly documented the usefulness of preoperative Chemotherapy in tumor shrinkage and thereby avoiding mutilating surgeries.[18]

An objective response to neo adjuvant chemotherapy in primary lesion provide important in vitro evidence that this therapy being used has antitumor activity. Tumor at remote sites will be sensitive as well.

Various chemotherapy combinations have been described in literature. Over all, clinical response rates vary in different studies between 60% to 90% one of the frequently used combination is 5 FU, Doxorubicin, cyclophosphamide.

In 1978, Bull et al showed a response rate of 82% to FAC regimen when compared with 62% response rate of 5–fluorouracil, methotraxate, cyclophosphamide.[11] In a study of 372 patients who received NACT with 4

cycles of FAC regimen Kuerer showed a complete in 12%.[12] Boti in the group containing 56 patients showed a response rate of 82%.[13]

The response rate in European organization for research and treatment of cancer breast corporative group trail (EOPTC) in 1991 using 4 cycles of pre-operative 5 –fluorouracil, epirubicin, cyclophosphamide was only 49%. Newer chemotherapeutic combinations with docetaxel have shown significant better response rates.[14]

Tables showing various trials and its results

AUTHORS	**No.of Patients**	**Drugs**	**Response**	**Complete Response**
Wolmark et al	1523	AC	80	13
Miller et al	40	A+D	85	16
Bear et al	805 804	AC+D AC	91 86	26 13

AC – Adriamycin, Cyclophosphamide

FAC – 5-fluorouracil, adriamycin and cyclophosphamide

D – Docetaxel

LABC WITHOUT ULCERATION

LABC WITH ULCER AND FUNGATION

RESPONSE ASSESSMENT

The assessment of response of tumor to Neo adjuvant chemotherapy is done by clinical and pathological tools. Clinically tumour response is mainly assessed by the modalities like physical examination, mammography, ultrasonography, CT Scan, MRI and PET Scan. Studies assessing the accuracy of these modalities have shown conflicting results. Herrada studying 100 patients compared clinical examination, ultrasonography and Mammography in the assessment of tumor response.[18] Physical examination was found to be the best predictor of size of primary tumor (p=0.0003) and its efficiency enhanced if combined with sonography (p=0.021).

In retrospective analysis of 189 patients, Chagpar et al found only moderate usefulness for clinical examination, USG, and mammography in picking residual tumor size after neoadjuvant chemotherapy with correlation coefficients slightly over 0.4 for all modalities.[19] Moyses et al studied the efficiency of CECT in the prediction of remaining tumour after NACT in 43 patients and found CECT measurement or residual tumor correlated satisfactorily with pathologic findings (correlation coefficient was 0.69).

However, clinical and mammographic correlations were globally unsatisfactory (0.49 and 0.28 respectively).[20]

In another study by Akashi et al concluded that Contrast enhanced computerised tomography is one of the best noninvasive technique for evaluating the extent of the remaining tumour tissue if cases of invasive lobular carcinoma and inflammatory breast carcinoma are excluded (R insertion mark 2-0.537).[21] CT scan has the advantage of easy availability and rapidity when compared to MRI.

WHO CRITERIA[22]

The antitumor activity of the chemotherapeutical agents is assessed by measuring the change in size of the tumor. The W.H.O. developed criteria to standardize clinical outcome in the early 1980's.

Complete Response

Complete absence of disease, signs, symptoms, and biochemical change made by the malignancy for one month, in which period nil new lesions arise.

Partial Response

Reduction of 50% or above in the total volume of clinically appreciable lesion lasting at least one month .

STABLE DISEASE – < 50% reduction.

Reduction or < 25% or above in the total volume of tumour of two perpendicular diameter of all measurable lesions, and absence of fresh lesions for eight wks.

PROGRESSION OR RELAPSE

Increase in the volume of the 2 perpendicular diameter of any measurable lesion by more than twenty five percent over the size present at early into the study. For those who respond over the size during at time of maximum falling off or the appearance of new areas of tumour spread.

However, WHO criteria is poorly reproducible as it does not describe methods used in measurement and selection of target lesions. In order to decrease the risk of measuring error and avoid overestimation of response rates response evaluation criteria in solid tumors (RECIST) working group proposed new guidelines.[23]

RESPONSE EVALUATION CRITERIA IN SOLID TUMORS WORKING GROUP (RECIST)

RECIST

Criteria offer a simplified, conservative, extraction of imaging data, for clinical trials. They presume that linear measures are an adequate substitute for 2-D methods and register 4 response categories.

Complete Response :	Complete abscence of all target lesions.
Partial Response :	Even thirty percent reduction in the sum of the Longitudinal diameter(LD) of target lesions, taking as reference the baseline sum LD.
Progressive Disease :	Even 20% increase in the total length of the Longitudinal diameter of target lesions.
Stable Disease :	Neither sufficient shrinkage to qualify for Partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longitudinal diameter since the treatment started.

LABC BEFORE SURGERY

LABC AFTER M R M

If greater than 10% of tumor cells stain positive for the nuclear receptor, the assay is reported as "positive" and a response to hormonal treatment is likely. There is no confirmatory evidence of receptor status as a useful indicator of response to NACT.

HER -2 NEU ONCOGENE

HER -2 / neu ocogene encodes a transmembrane tyrosine kinase that is the receptor for a family of polypeptide growth factors, Over expression implies elevated tumor behaviour, raised recurrence rates, and increased number of death in patients with positive nodes.[32]

Zhang F et al., could not monitor a correlation between human epidermal growth factor-2 expression and the clinicopathological response to NACT in 97 patients with carcinoma breast.[33] Several other studies have found a positive correlation between the expression of this oncogene with response to anthracycline based chemotherapy.

The HER -2 / neu is used as a indicator, in deciding efficacy to trastuzumab in the distant metastasis. Currently available data shows an adriamycin – based regimen to be more effective in HER -2 / neu – over expressing tumours.

TOMOUR PROLIFERATION MARKER : Ki 67

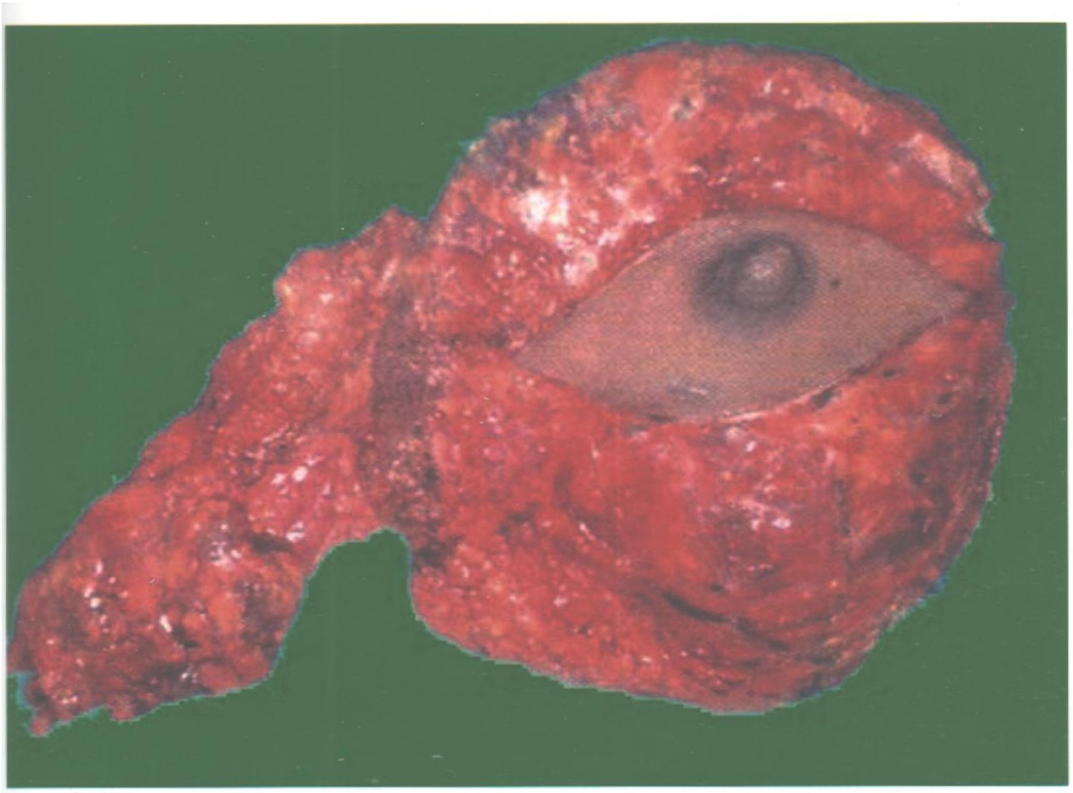
Uninhibited proliferation, which is the main feature in malignant transformation, can be quantified by assessing the group of cells that are committed to succeeding to cell cycle. Monitoring the presence of Ki 67 by immunohistochemistry correlates with the S phase fraction. Petit et al evaluated the grade of tumour, Ki-67, hormonal receptors, human epidermal growth factor receptor -2 and topoisomerase II alpha status as useful indicators in carcinoma breast patients managed with NACT with anthracycline . In 119 patients, the clinical outcome (OR) was 80%, and of complete responders (CR) was 19%. In the multivariate analysis, the absence of HER-2 neu expression and Ki-67 > or = 20% is a useful tool for a clinically complete response.[30]

P^{53}

P^{53} also known as the "guardian of the genome", is a transcription factor, which regulates the apoptosis. P^{53} has been shown to induce apoptosis, whereas loss P^{53} action has documented to increase cellular resistance to a number of chemotherapeutic agents. Hence, it has been used in various studies as a marker of response to chemotherapy. The results are conflicting and it relates to the type of chemotherapeutic drug used.

Kandioler-Eckersberger D et al studied the p^{53} status of 67 patient's breast tumour using both immunohistochemistry (IHC) and direct sequencing of the entire p^{53} gene. Of 17 patients with treatment failure, seven had a P^{53} mutation and 14 had a positive immunohistochemistry. Only one of seventeen patients not showing any response to management had neither a mutation nor positive immunohistochemistry. In the FEC group, treatment failure was related to both the existence of P^{53} gene mutation (P=0.0029) and a positive IHC (P=0.0001) and these may help to predict resistance to anthracyclines in breast cancer. Anelli et al studied the response of breast cancer in 73 patients treated with paclitaxel and adriamycin. They found, the absent p^{53} expression denotes a higher chance of responding to this regimen.

However, many studies analysing p53 status by use of IHC have failed to show a analytical value of p^{53} in breast cancer.



SPECIMEN OF LABC

MATERIALS AND METHODS

The study was done during the period from January 2011 to June 2012 in the department of Surgery Thanjavur Medical college and Hospital Thanjavur. All the patients with Breast cancer was examined clinically. Patients with LABC was selected for the study.

Locally advanced carcinoma breast was defined as per AJCC staging and included stage IIb (T_3 N_0M_0) Stage III A and stage III b tumours. Exclusion criteria included any contraindications for chemotherapy.

INCLUSION CRITERIA

- Stage IIb (T3N0M0)
- Stage IIIa
- Stage IIIb
- LABC without any co-morbid conditions

EXCLUSION CRITERIA

- All early Breast Recurrence
- LABC with Distant metastasis
- LABC with co morbid conditions
- Any contra indications for surgery

INVESTIGATIONS

- Complete Haemogram
- Renal Function Tests
- Liver Function Tests
- FNAC
- X-Ray Chest
- ECG
- Ultrasonogram Abdomen
- Echocardiogram

FNAC was done to confirm the diagnosis, in all patients. Routine investigations like complete hemogram, renal function tests, and liver function tests were done. Metastatic work up was done, X-Ray chest and ultrasonogram abdomen. Cardiac assessment was done with echocardiogram for adriamycin based chemotherapy.

Detailed history and clinical examination of the patients were carried out as per the proforma. Tumor size assessed clinically two longest perpendicular diameter and the products of the two perpendicular diameters

were calculated. All Patients have taken CT scan breast before starting Neo adjuvant chemotherapy.

After completion of 1st cycle and before starting a next cycle C.T. breast taken to measure the Breast size. After completion of 3 cycles at the end of 3rd week, tumor size measured clinically and C.T.Breast taken regularly.

Chemotherapy was administered after admitting the patients after calculating body surface area. Antiemetic pre medications which included ondensetron. 4 mg, Injection dexamethesone 8 mg. and ranitidine 150mg./sq.m.

Intravenous infusions of cyclophoshamide 600mg/m^2 5 fluorouracil 500mg/m^2, adriamycin 60mg/m^2. were given as per FAC regimen. Patients were observed for side effects and discharged on same day with oral ondensetron prescription for 3 days.

Chemotherapy was repeated every 21 days after assessing the tumor response clinically for maximum of three cycles. After two weeks of the last preoperative cycle, tumour size was assessed clinically and with a repeat C.T Breast. RECIST criteria was used to assess the tumor response clinically. Patients with partial response were worked up for modified radical

mastectomy. The mastectomy specimens were assessed in patients who showed complete clinical response. All specimen showed tumor free margins.

Patients who had complete clinical response according to WHO / RECIST criteria were managed with modified radical mastectomy. Patients who showed no response according to WHO / RECIST criteria were managed with Toilet mastectomy followed with adjuvant chemotherapy and Radiotherapy.

DOSAGE AND SCHEDULE38

Choosing the regimen

There is no single regimen that has emerged as the treatment of choice. Several trials have demonstrated that a 10% - 20% higher response rate has been observed with Doxorubicin/Epirubicin containing regimen with an increase in median survival from 14-18 months and an increase in median time of treatment failure from 5 to 7 months. The shorter duration of regimen and relative ease of administration has led to the popularity of AC regime and favor this regimen as the first choice of therapy.

Regimens

FAC

- 5 FU 500mg/m2
- Adriamcycin 60mg/m2
- Cyclophosphamide 600mg/m2
- On day one every 3 weeks for 6 weeks

AC

- Adriamycin: 60mg/m2, D1
- Cyclophosphamide: 600 mg/m2, D1
- 4 cycles are given, once every 3 weeks

CAF

- Cyclophosphamide: 100 mg/m2 d, D1-14
- Adriamycin : 30 mg/m2, D1, 8
- 5 FU: 500mg/m2, D1, 8
- 6 cycles are given, once in 4 weeks

CMF

- Cyclophosphamide: 750 mg/m2
- Methotrexate : 50 mg/m2
- 5-FU: 600 mg/m2
- Given once in every 3 weeks, for 6 cycles.

FEC

- 5 FU 500mg/m2
- Epirubicin 50mg/m2
- Cyclophosphamide 500mg/m2
- On day one, every 3 weeks for 6 cycles

TAC

- Docetaxel 75 500mg/m2 on D1
- Adriamycin 50mg/m2 on D1
- Cyclophosphamide 500mg/m2 on D1
- 6 cycles are given, every 3 weeks.

AC-T

- Adriamycin : 60mg/m2, D1
- For 4 cycles once every 3 weeks
- Followed by
- Taxol (paclitaxel) 175mg/m2
- Every 3 weeks for 4 cycles

RESULTS

The study was conducted between 2011 August and november 2012. Seventy two patients who qualified for the inclusion criteria were included in the study. Three patients were excluded as the pre chemotherapy X-Ray revealed lung metastasis. Four patients lost follow up. Five patients defaulted after 3 cycles of chemotherapy. Hence 9 patients out of 69 did not complete the treatment. 60 patients who were included in the study completed the treatment.

DEMOGRAPHIC PROFILE

Clinical parameters of 72 patients were analysed. The range of patients age was 32 to 72 years and mean age at appearance was 55.45 years. 6.9% patients were in the age group of < 40 years. 16.6% patients fell in the age group of 40-49 years & 50% fell in the age group of 50 to 59 years. 26.5% were above 60 years. Fifty two patients in the study group were post menopausal and 20 patients were pre menopausal.

There was a predominance of left sided Breast cancer. Thirty nine (54.2%) patients had cancer of the left Breast where as thirty three patients had right sided Breast cancer (45.8%). Thirty five patients (48.9%) had

upper outer quadrant of the Breast. Six patients (13.93%) had tumour in the central quadrant.

Thirty four patients (47.22%) had T3 tumor at presentation whereas 38 patients (52.78%) had T4 presentation.

Seven (9.72%) patients had stage IIb disease. Whereas 27 patients (37.5%) and III-a, Thirty eight (52.78) patients had III b. The mean size of the tumor in its longest diameter was 7.04 cms.

COMPLICATIONS

Alopecia and vomiting were the commonest side effects noted in the study. All the patients developed Alopecia of varying intensity. 50 patients had Black discoloration of nails, palms. Five patients developed anemia that was managed with Hematinics and transfusion.

Primary tumor response to neoadjuvant chemotherapy

65 patients were finally assessed for study of NACT in locally assessed Breast cancer. Out of sixty five, six patients (9.24%) had complete response. Thirty six patients (55.38%) patients had partial response and 23 patients (35.36) had no response according to RECIST criteria.

TABLE -1

AGE DISTRIBUTION AMONG THE PATIENTS IN THE STUDY GROUP

Age	No. of Cases	Percentage (%)
<40	5	6.9
40-49	12	16.6
50-59	36	50
>60	19	26.5
Total	72	100

/

CHART -1

AGE DISTRIBUTION AMONG THE PATIENTS IN THE STUDY GROUP

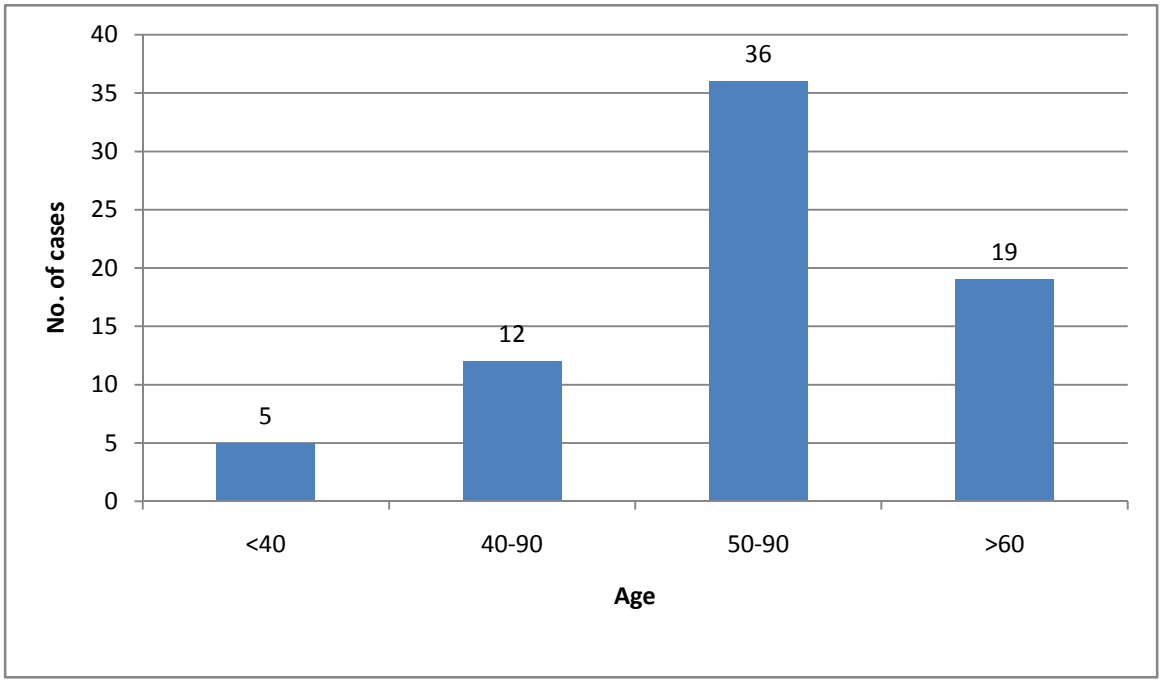


TABLE -2

QUADRANT DISTRIBUTION AMONG THE PATIENTS IN THE STUDY GROUP

Quadrant	No.of Cases	Percentage (%)
UO	35	48.6
LO	17	23.6
C	10	13.92
UI	7	9.7
LI	3	4.18
Total	72	100

CHART -2

QUADRANT DISTRIBUTION AMONG THE PATIENTS IN THE STUDY GROUP

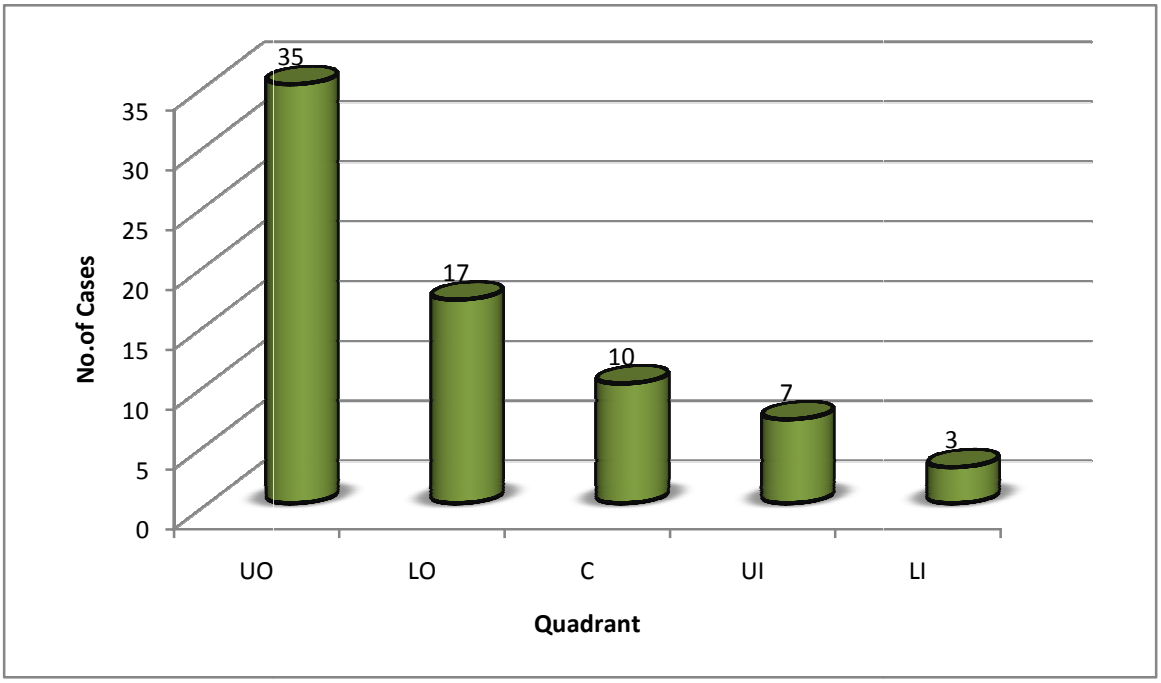


TABLE -3

SIDE DISTRIBUTION AMONG THE PATIENTS IN THE STUDY GROUP

Side	No.of Cases	Percentage (%)
Right	33	54.2
Left	39	45.8
Total	72	100

TABLE -4

DISTRIBUTION OF PATIENTS ACCORDING TO TNM CLASSIFICATION

TNM Classification	No.of Cases	Percentage (%)
$T_3N_0M_0$	7	9.72
$T_3N_1M_0$	23	31.94
$T_3N_2M_0$	4	5.55
$T_{4b}N_0M_0$	5	6.94
$T_{4b}N_1M_0$	25	34.75
$T_{4b}N_2M_0$	5	6.94
$T_{4b}N_2M_1$	3	4.16
Total	72	100

CHART -3

DISTRIBUTION OF PATIENTS ACCORDING TO TNM CLASSIFICATION

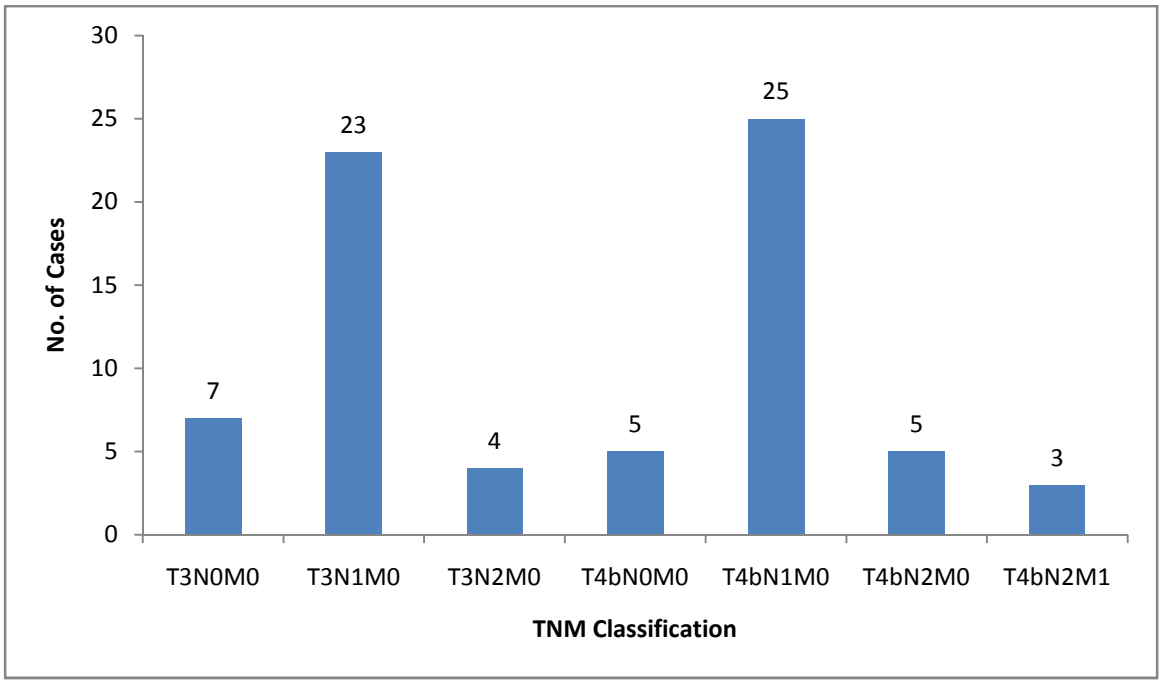


TABLE -5

DISTRIBUTION OF PATIENTS ACCORDING TO T-STAGING OF TNM CLASSIFICATION

	No.of Cases	Percentage (%)
T_3	34	47.22
T_4	38	52.78
Total	72	100

CHART -4

DISTRIBUTION OF PATIENTS ACCORDING TO T-STAGING OF TNM CLASSIFICATION

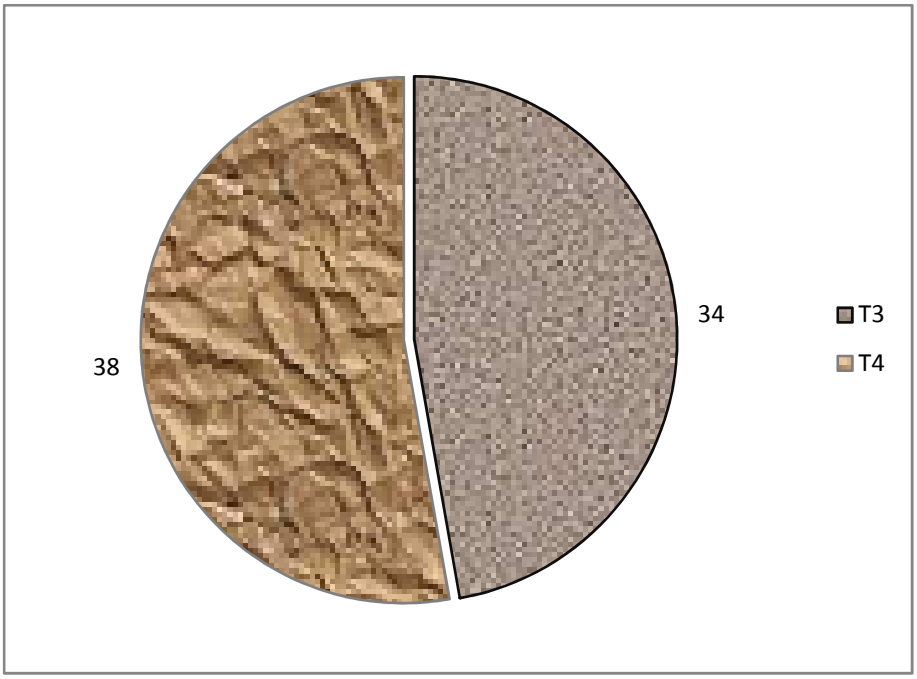


TABLE -6

DISTRIBUTION OF PATIENTS ACCORDING TO CLINICAL STAGING

Stages	No.of Cases	Percentage (%)
Stages IIb	7	9.72
Stage IIIa	27	37.50
Stage IIIb	38	52.78
Total	72	100

CHART -5

DISTRIBUTION OF PATIENTS ACCORDING TO CLINICAL STAGING

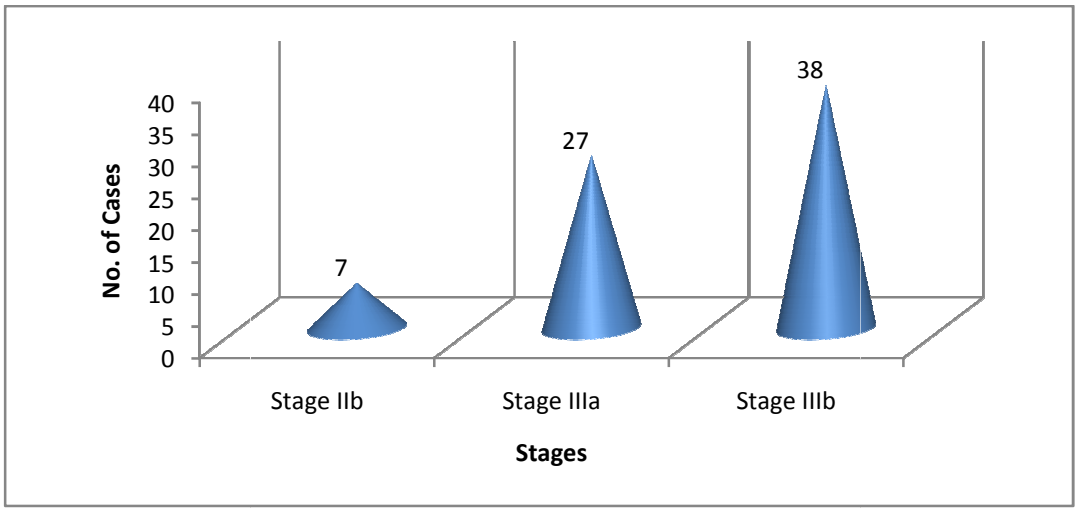


TABLE -7

RESPONSE RATE OF NACT ACCORDING THE RECIST CRITERIA

Response	No.of Cases	Percentage (%)
Complete	6	9.24
Partial	36	55.38
No Response	23	35.38
Total	65	100

CHART -6

RESPONSE RATE OF NACT ACCORDING THE RECIST CRITERIA

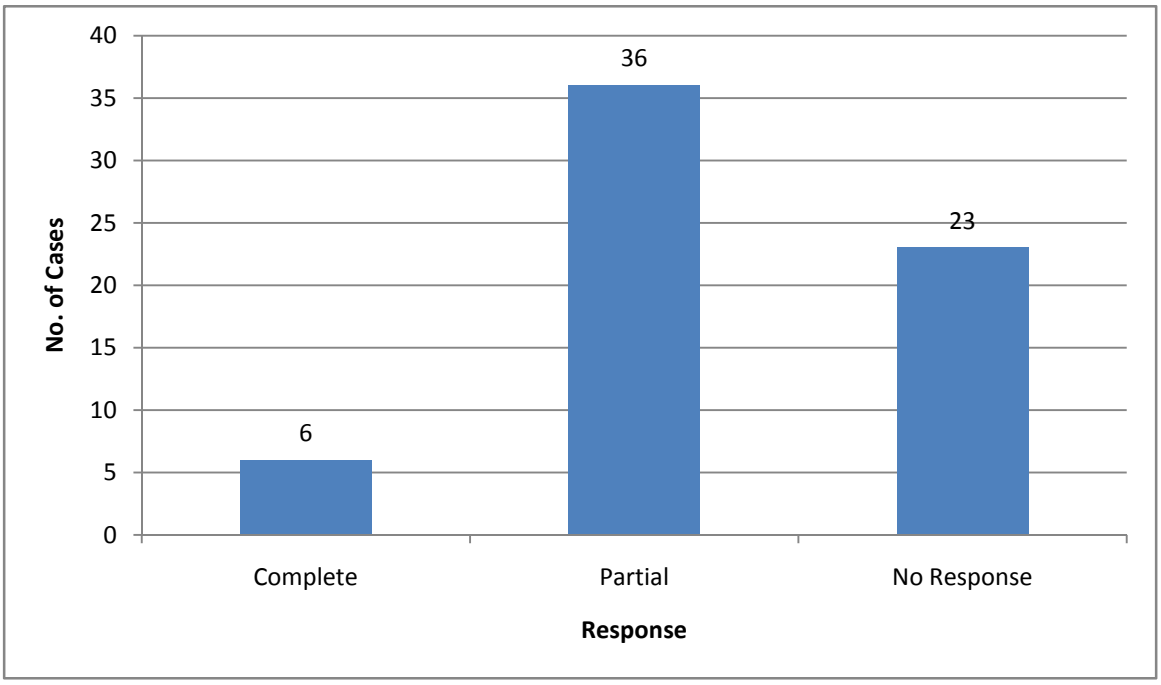


TABLE -8

TYPE OF SURGERY DONE

Surgeries	No.of Cases	Percentage (%)
Modified Radical Mastectomy	47	78.33
Toilet Mastectomy	13	21.67
Total	60	100

CHART -7

TYPE OF SURGERY DONE

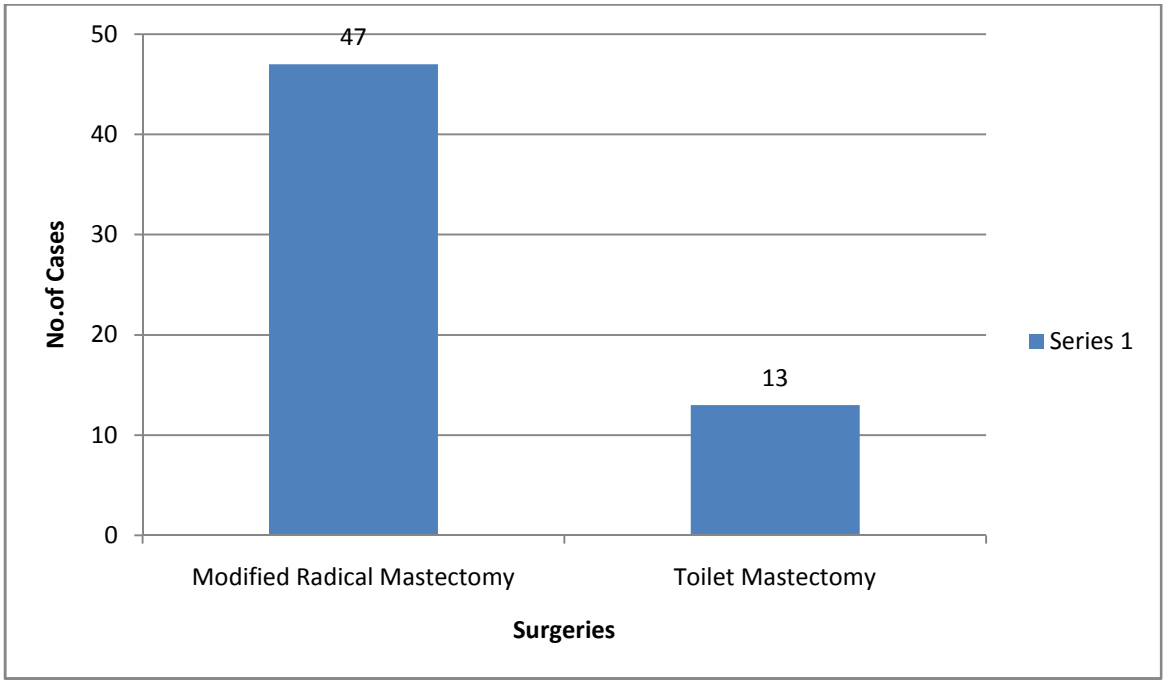


TABLE -9

DISTRIBUTION OF PATIENTS ACCORDING TO SIZE OF TUMOUR

Mean size of Tumour for

Complete Response	:	5.53
Partial Response	:	6.33
No Response	:	8.83

Mean	:	Before NACT	After NACT
		7.04	3.54

DISCUSSION

Over the last decades Neo adjuvant Chemotherapy has changed the way in which locally advanced carcinoma breast is managed.

The study was designed with the aim of assessing the efficacy of Neo adjuvant chemotherapy in the population in and around TMCH, THANJAVUR

An objective response to neo adjuvant chemotherapy in primary lesion provides important in vitro evidence that this therapy being used has antitumor activity. Tumor at remote sites will be sensitive as well.

Various chemotherapy combinations have been described in literature. Over all, clinical response rates vary in different studies between 60% to 90% one most commonly used combination is 5-fluorouracil, adriamycin, cyclophosphamide.

In 1978, Bull et al showed a response rate of 82% to FAC regimen when compared with 62% response rate of 5-fluorouracil, methotraxate, cyclophosphamide. In a study of 372 patients who received NACT with four

cycles of FAC regimen Kuerer showed a complete response in 12%. Boti et al in fifty six patients showed an overall outcome of 82%.

The response rate in European organization for research and treatment of cancer breast corporative group trial (EORTC) in 1991 using 4 cycles of pre-operative 5 – fluorouracil, epirubicin, cyclophosphamide was only 49%. The recent introduction of chemotherapy regimens using docetaxel have been shown to have significant better response rates. Expecting same line of better results we have followed F.A.C regimen in our study in TMCH, Thanjavur.

Seventy two patients with LABC breast were included in the study. Three patients have metastasis in the X-Ray chest. Four patients lost follow up. Five patients did not undergo mastectomy. Finally sixty patients completed the treatment protocol.

The reasons for this drop out could be the need for multiple hospital visits and side effects of the chemotherapy. Even in western studies like

NSABP B – 27 only 80% of the total patients inducted in the study had completed the treatment.

DEMOGRAPHIC PROFILE

The mean age at presentation to hospital 55.45 years with majority in 50-59 years. The mean longest diameter of tumor at presentation in this study was 7.04 and after NACT was 3.54.

RESPONSE TO NEO ADJUVANT CHEMOTHERAPY

All patients with LABC received three cycles of FAC regime with cyclophosphamide 600mg/m^2. 5FU 500mg/m^2, adriamycin 60mg/m^2 at intervals of 21 days.

In a study on preoperative chemotherapy conducted in patients with operable breast cancer, a response rate of 80% and complete pathologic response in 13% was seen.

The following are taken as predictor of response.

i. Clinical : The size of Tumor.

Grave signs such as oedema and ulceration. Nodal Status : Size Number, Group and fixity of Tumor.

ii. Epithelial elements i.e. FNAC

Expression of differentiation of neoplastic cells Grading and outcome pre and post operatively size and shape staging of neoplasam.

iii. Investigations :

- CT chosen, as it is the most accurate non – invastive technique of identifying the extent of residual carcinoma.
- LFT is repeated to find out any rise in Alkalaine phosphatase.
- X-Ray used as the pre and post op.skeletal survey.

SIZE AS A PREDICTOR OF RESPONSE

The mean size of tumor in patients with complete response was 5.53, 6.33 for partial response, and 8.83 for no response.

Kuerer et al has found smaller tumor is associated with a complete pathological response in 372 patients receiving adriamycin based neo adjuvant chemotherapy (P.value <0.01). The size of the primary tumor has also been found to be associated with survival.

Valagussa shown the five year survival rate were 65%, 36%, 16% for tumor volume measuring <5cm, 5-10cm and >10cm respectively.

After completion of three cycles of NACT the tumor size grave signs like oedema and ulceration decreased in 78% of cases fixity became less.

AXILLARY NODE STATUS AND RESPONSE

Patients with clinically negative axilla had a significantly better chance of having complete response than that in patienst with clinically positive axilla. Out of 48 patients who were node positive 20 patients became clinically negative after completion of 3 cycles of chemotherapy. In the remaining 28 patients size of the node and their number has decreased. Among the specimen of 28 patients, 10 were less than 2 node positive for

tumor. 18 were positive for more than 4 nodes. Node positive patients were treated with adjuvant chemotherapy and radiotherapy.

SKIN INVOLVEMENT AND RESPONSE

Tumors without skin involvement showed a significantly better response to chemotherapy assessed by W.H.O. criteria. The better response shown by tumors with smaller size clinically node negative and no skin involvement suggest that tumor cells may became more resistant as the tumor grows.

This is in concordance with the Goldie – cold man Hypothesis that the likehood that resistant cells are present is a function of tumor size (or) the number of tumor cells and the spontaneous mutation rate of the cells. Histologically all the tumours turned out to be infiltrating ductal carcinoma.

This study shows that the NACT with FAC regimen effects dramatic regression of the Breast lesion in apparently 70% to 80%. The index lesion

and axillary metastasis have disappeared following the 3 cycles of FAC regimen.

The study also shows that the tumor shrinkage and disappearance increased the sense of well being among of the patients, their confidence level enhanced: After the NACT Technical operability of the tumor has improved What seemed:- Inoperable become Amenable to modified radical mastectomy in 60 to 70% of patients.

SURGERY

Out of sixty patients who had completed the 3 cycles of Neo adjuvant chemotherapy. Six patients (10%) who had complete response underwent modified radical mastectomy. The other forty one patients (68.33%) also underwent modified radical mastectomy totally accounting for 78.33% and remaining 13 patients (21.6%) underwent Toilet mastectomy.

After establishing the loco regional control by above surgeries, these patients were followed up by adjuvant chemotherapy and adjuvant radiotherapy.

CONCLUSION

- Locally advanced Cancer Breast tops among all the Carcinoma Breast attending surgical outpatient department in TMCH,THANJAVUR.

- Locally advanced Cancer Breast with axillary node and grave signs like oedema and ulceration is one of the presentation among all Carcinoma patients attending surgical Outpatients of TMCH,THANJAVUR.

- After Neo adjuvant chemotherapy for LABC with FAC regimes most of the Inoperable advanced Breast cancer became Technically operable.

- Appropriate surgery done with or without post operative events in 78% of patients who became symptom free, and their quality of life improved. Survival period is prolonged and their disease free survival also improved.

- 68.3% patients who partially responded after Neo adjuvant chemotherapy were managed by M.R.M. 10% patients who

responded completely also managed with modified radical mastectomy. 21.6% patients who are non responders clinically after Neo – adjuvant chemotherapy are treated with Toilet mastectomy.

- In a nut shell neo adjuvant chemotherapy for locally advanced Breast cancer definitely paves the way for successful surgery in most cases, there by making patients free from agonizing symptoms, giving satisfactory quality of life without much burden to the individual, family & society.

BIBILIOGRAPHY

1. Essential Surgical Practice by Cushieri, 4th Edition, p.85-86.
2. Sabiston Text Book of Surgery, 18th Edition, p.872-75.
3. Schwartz Text Book of Surgery, 7th Edition, p.
4. Principles and Practice of Oncology, Devitta, 7th Edition, p.1451.
5. Essential of Medical Pharmacology, 5th Edition, p.771-776.
6. Fischer B.Personal work in breast cancer research and management, 1996; 23(4); 414-427.
7. Bonadonna G.,., Valagussa P., Combination Chemotherapy as an adjuvant treatment in operable breast cancer. N.Engal J Med 1976; 294; 405-410.
8. Fischer B., Carbone P., et sl. L-phenylalanine mustard (L-PAM) in the treatment of primary breast cancer, N Engal J Med 1975; 292: 117-122.
9. Gianni L., Valagussa P., Bonadonna G. Adjuvant and neoadjuvant treatment of breast cancer. Semin Oncol 2001. Feb; 3-29.
10. Wolmark N., Wang J., Mamounas E., Neoadjuvant chemotherapy in patients with operable breast cancer: nine – year results from National Surgical Ahjuvant Breast and Bowel Project B – 18. J Natl Cancer Inst Monogr 2001: (30) : 96-102.

11. Bull JM, Carbone PP, Bolm J, et al., A randomized comparative trial of adriamycin versus methotrexate in combination drug therapy. Cancer 1978 May; 41(5): 1649-57.

12. Kurerer HM, Newman L A, Smith T L, Falkson G, Ames FC. Hunt KK, Dhingra K, et al. Clinical course of breast cancer patients with complete pathologic primary tumor and axillary lymph node response to adriamycin– based NACT. Oncol. 1999; 17: 460-469.

13. Botti C, Vici P, Lopez, Cavaliere R, et al. Prognostic value of lymph node metastases after NACT for large-sized operable carcinoma of the breast. J.Am Coll Surg 1995 Sep; 181(3) 202-8.

14. Van der Hage J, Van de Velde Velde CJH, J.Clin. M, Scinto AF, Cognetti F ,Julien JP, Tubiana – Hulin M, Vandervelden C, Duchateau L et al. Preoperative Chemotherapy in Primary Operable Breast Cancer: Results from the European Organization for Reseach and Treatment of Cancer Trial 10902. Journal of Clinical Oncology 2001; 19(22): 4224 - 4237.

15. Arimappamagan A, Kadambari D., , Elangovan S, Reddy K SN. Complete axillary conversion after NACT in LABC: A step towards conserving axilla? Indian J Cancer 2004; 41(1): 13-17.

16. Miller KD, Stevens WM, , Monaco F, Seshdri R, et al. Combination Versus Sequential adriamycin and Docetaxel as Primary Chemotherapy for Breast Cancer : A Randomized Pilot Trial of the Hoosier Oncology Group. Journal of Clinical Oncology 1999; 17(10):3033-3037.
17. Bear HD, Anderson S, R, Mamounas P, Fisher B, et al. The effect on tumour response of adding preoperative docetaxel to preoperative adriamycin and cyclophosphamide : preliminary results from National Surgical Adjuvant Breast and Bowel Project protocol B-27. J Clin Oncol 2003; 21(22):4165-74.
18. Herrada J, Iyer RB,. Relative value of physical examination, mammography, and breast sonography in evaluating the size of the primary tumour and regional lymph node metastases in women receiving NACT for LABC. Clin Cancer Res. 1997; 3:1565-1569.
19. Chagpar AB, Middleton LP, Sahin AA, , Mirza An et al. Accuracy of Physical examination, ultrasonography, and mammography in predicting residual pathologic tumour size in patients treated with neoadjuvant chemotheraphy. Ann Surg 2006 Feb; 243(2):257-64.

20. Moyses B, Haegele P, Rodier JF, et al. Assesment of response by breast helical computed tomography to NACT in large inflammatory breast cancer. Clin Breast Cancer 2002 Jan; 2(4):304-10.

21. Akashi-Tanaka S, Fukutomi T, Watanabe T, et al Lehmann S, Petit T, Velten M. Accuracy of CECT in the prediction of residual cancer after neoadjuvant chemotherapy. Int J Cancer 2001; 96:66-73.

22. Miller AB, Hoogstraten B, Staquet M, Winker A. Reporting results of cancer treatment. Cancer 1981; 47:207-14.

23. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumours. J. Natl. Cancer Inst 2000; 92:205-16.

24. Kimura M, Tominaga T. Lehmann S, Petit T, Velten M Outstanding problems with response evaluation criteria in solid tumours (RECIST) in breast cancer. Breast cancer 2002; 9:153-9.

25. Park JO, Lee SI, Song SY, , et al. Measuring Response in Solid Tumours: Comparison of RECIST and WHO Response Criteria. Jpn J Clin Oncol 2003; (33);533-7.

26. Bloom HJ, Richardson WW. Histological grading and prognosis in breast cancer: A Study of 1409 cases of which 359 have been followed for 15 years. Br J Cancer 1957; 11:359-377.

27. Le Doussal V, Tubiana-Hulin M, Kim K, Kim WS, Jung CW, FriedMan S et al. Progonostic value of histologic grade nuclear components of Scarff-Bloom-Richardson (SBR). An improved score modification based on a multivariate analysis of 1262 invasive ductal breast carcinomas. Cancer 1989; 64:1914-1921.

28. Colleoni M, Minchella I, Mazzarol A, et al. A response to primary chemotheraphy in breast cancer patients with tumours not expressing estrogen and progesterone receptors. Ann. Oncol 2000; 11:1057-1059.

29. Lippman ME, Allegra JC, Thompson EB, Simon R G, Nole F, Peruzzotti G, Rocca, Barlock A, Green L, et al. The relation between estrogen receptors and response rate to cytotoxic chemotheraphy in metastatic breast cancer. N. Engl. J. Med1978; 298:1223-1228.

30. Petit T, Wilt M, Velten M, Comparative value of tumour grade, hormonal receptors, Ki-67, HER-2 and topoisomerase II alpha status as predictive markers in breast cancer patients treated with neoadjuvant anthracycline-based chemotherapy. Eur J Cancer 2004 Jan; 40(2):205-11.

31. Bonnefoi H, Diebold-Berger S, Therasse P, Hamilton A, Millon R, Rodier JF, Borel C, et al. Van de Vijver M, MacGrogan G et al., Locally advanced/ inflammatory breast cancers treated with intensive epirubicin-based neoadjuvant chemotherapy: are there molecular markers in the primary tumour that predict for 5 –year clinical outcome? Ann. Oncol 2003; 14:406-413.

32. Slamon DJ, Clark GM, Wong SG et al. Human breast cancer: Correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science 1987; 235:177-182.

33. Zhang F, , Kuerer HM et al. Correlation between HER2 expression of breast cancer and response to neoadjuvant chemotherapy. Cancer 2003, 97(7):1758-1765.

34. Hamilton A, Piccart M: Yang Y, Smith T, Kau SW, Esteva FJ The contribution of molecular markers to the prediction of response in the treatment of breast cancer: A review of the literature on HER-2, p53 and BCL-2. Ann Oncol 2000; 11:647-663.

35. Yamauchi H, Stearns V, Hayes DF. When is a tumour marker ready for prime time? A case study of c-erbB-2 as a predictive factor in breast cancer. J Clin Oncol 2001; 19-2334-2356.

36. Kandioler-Eckerberger D, Ludwig C, Rudas M, Kappel S, Janschek E, Wenzel C et al. TP53 mutation and p53 over expression of prediction of response to neoadjuvant treatment in breast cancer patients. Clin, Cancer Res 2000; 6:50-56.

37. Aneli A, Brentani RR, Gadelha AP et al. Correlation of p53 status with outcome of neoadjuvant chemotherapy using paciltaxel and doxorubicin in stage IIIB breast cancer. Ann Oncol 2003; 14:428-432.

38. Bonetti A, Zaninelli M, Leone R, Cetto GL, Pelosi G, Biolo S, et al. BCL-2 but not p53 expression is associated with resistance to chemotherapy in advanced breast cancer. Clin. Cancer Res 1998; 4:2331-2336.

PROFORMA

Name

Age & Sex Code No:

Address I.P. No:

I.D No.

History

i) Duration of lump

ii) History of benign Breast disease

iii) Family History of 3 generations

a) Grand Mother

b) Mother/Aunts

c) Sisters

MENTRUAL HISTORY

i) Pre menopausal

ii) Post menopausal

COMORBID DISEASE

CLINICAL EXAMINATIONS

STAGE OF DISEASE BY TNM BEFORE CHEMOTHERAPY

STAGE OF DISEASE BY TNM AFTER CHEMOTHERAPY

INVESTIGATIONS

- Xray Chest
- USG Abdomen
- LFT
- FNAC/True cut Biopsy
- U.S.G. Breast
- C.T. Breast

SIDE EFFECTS OF THE CHEMOTHERAPY

RESPONSE ASSESSMENTS

i) Clinical Response

ii) U.S.G Based

iii) CT Based

SURGERY PLANNED

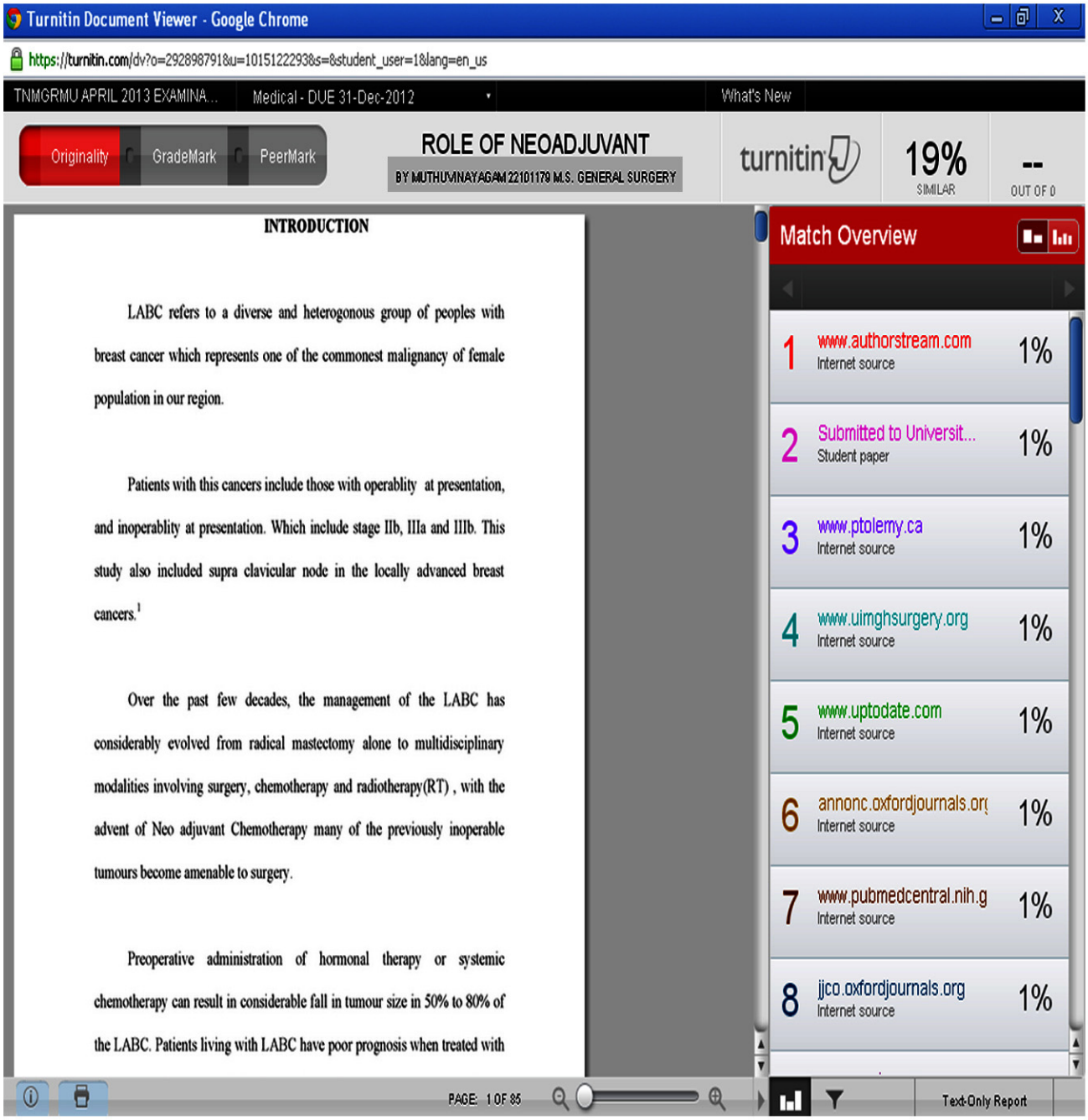
- Simple Mastectomy
- Modified Mastectomy
- Toilet Mastectomy

S.NO	NAME	Age Set	I.P.NO	SIDE	TNM STAGING	Tumour size before nact	Tumour size after NACT	HPE	U.S/C.T	Surgery
1	Kasthuri	32	1374927	R	T3N2M0	5x5.7		IDC	C.T	MRM
2	Sharmila	43	1381018	R	T4bN0M0	8x7.1	4x3.1	IDC	C.T	MRM
3	Selvi	47	1387334	R	T4bN0M0	8x7.1	5.4x4.5	IDC	C.T	TM
4	Ammuni	45	1391296	R	T3N0M0	5.5x6	2x1	IDC	C.T	MRM
5	Vaduvammal	55	1403147	L	T4bN1M0	8.8x8	4.4x4	IDC	C.T	MRM
6	Ranjitham	35	1412541	L	T3N1M0	8x8.5	3x4.6	IDC	C.T	MRM
7	Preetha	61	1420801	R	T3N1M0	5.9x5.5		IDC	C.T	MRM
8	Susila	54	1393514	R	T3N1M0	6.5x6	3x3	IDC	C.T	MRM
9	Vasantha	31	1395330	L	T3N1M0	5x6.0	2x3	IDC	C.T	MRM
10	Thangavel	69	1396009	R	T4bN0M0	8x8	3.8x4	IDC	C.T	MRM
11	Marry	54	1422688	L	T3N1M0	10x10	5x6	IDC	C.T	MRM
12	Saroja	33	1028097	L	T3N2M0	5x5.2		IDC	C.T	TM
13	Chellammal	58	1033259	R	T3N1M0	6x5	3x2.5	IDC	C.T	MRM
14	Gangammal	72	1034900	L	T4bN1M0	6x6.5	3x2	IDC	C.T	MRM
15	Selvanayaki	36	1035346	R	T3N2M0	6.5x6	2x3	IDC	C.T	MRM
16	Amutha	65	103641	R	T4bN1M0	7x6.4	3.5x3.2	IDC	C.T	MRM
17	Rajamani	42	1062449	L	T4bN0M0	9x7	4.5x4.8	IDC	C.T	TM
18	Rani	64	1064003	R	T3N2M0	6.7x7	3.4x3.5	IDC	C.T	MRM
19	Alli	51	1067693	L	T4bN1M0	8.2x7	4x3.5	IDC	C.T	MRM
20	Thenmozhi	57	1041082	L	T4bN0M0	8x7	4.4x3.9	IDC	C.T	TM
21	Saroja	56	1351357	R	T4bN1M0	8.5x7.4	4x3.1	IDC	C.T	MRM
22	Dhanalakshmi	59	1356137	L	T3N0M0	5x5.8		IDC	C.T	MRM

S.NO	NAME	Age Set	I.P.NO	SIDE	TNM STAGING	Tumour size before nact	Tumour size after NACT	HPE	U.S/C.T	Surgery
23	Chandra	69	1357195	R	T4bN1M0	5x3	2x1.3	IDC	C.T	MRM
24	Kanaga jeyam	47	1360291	L	T4bN1M0	8x8.5	4x4.2	IDC	C.T	MRM
25	Santha	54	13601404	R	T3N1M0	8x5.8	3.8x4	IDC	C.T	TM
26	Mala	64	1365820	L	T3N0M0	6x4	3x2	IDC	C.T	MRM
27	Panchavarnam	57	1368513	R	T4bN1M0	7.5x7	3.5x3.5	IDC	C.T	MRM
28	Rajalakshmi	71	1377327	L	T3N1M0	5x5.1		IDC	C.T	MRM
29	Arokya mary	63	1383626	R	T4bN1M0	8.6x8	4.4x4.2	IDC	C.T	MRM
30	Ayiranvalli	58	1384888	L	T3N1M0	4x3	2x1.5	IDC	C.T	MRM
31	Mookayi	48	1385488	R	T4bN1M0	9.8x7.2	5x4	IDC	C.T	TM
32	Chipa	52	1387499	L	T3N1M0	5x4	2.5x2	IDC	C.T	MRM
33	Ponnarani	55	1391401	R	T3N1M0	4x4	1.5x2	IDC	C.T	MRM
34	Subalaxmi	54	1401423	R	T3N1M0	6x5	3x2	IDC	C.T	MRM
35	Santha	65	1407112	L	T4bN1M0	9.8x7	6.5x3.4	IDC	C.T	TM
36	Chinnathal	40	1412862	R	T3N1M0	7x5	3.5x2	IDC	C.T	MRM
37	Jeenath begam	54	1416167	R	T3N1M0	8x4.5	4.3x2.4	IDC	C.T	MRM
38	Purphavalli	53	1388094	L	T4bN1M0	4x3.5	2x1.4	IDC	C.T	MRM
39	Mahamayee	66	1389444	L	T3N1M0	5x4	2.5x1.2	IDC	C.T	MRM
40	Irudaya mary	48	1396191	R	T4bN1M0	10x7.3	6.1x4.2	IDC	C.T	TM
41	Revathy	67	139906	R	T4bN1M0	9x6.4	5.2x4	IDC	C.T	TM
42	Amarya	51	1399176	L	T3N0M0	5.5x5		IDC	C.T	MRM
43	Rajam	52	1403687	L	T4bN1M0	6x3.2	2x1.1	IDC	C.T	MRM
44	Vijaya	55	1411006	L	T4bN2M0	6.3x4	3.2x1.5	IDC	C.T	MRM

S.NO	NAME	Age Set	I.P.NO	SIDE	TNM STAGING	Tumour size before nact	Tumour size after NACT	HPE	U.S/C.T	Surgery
45	Varammal	46	1414818	R	T4bN1M0	9x6.2	5x4.2	IDC	C.T	TM
46	Pooja	58	1419711	R	T4bN1M0	9x3.2	5.4x2.2	IDC	C.T	MRM
47	Magadevi	53	1422994	R	T3N0M0	5.6x3	2x1.2	IDC	C.T	MRM
48	Rani	62	1360775	L	T4bN1M0	7x5.2	4x3.2	IDC	C.T	TM
49	Uma	41	1389729	L	T3N1M0	5x6	2x1.8	IDC	C.T	MRM
50	Santhi	57	1390415	R	T3N1M0	6.1x6.5	3x2.5	IDC	C.T	MRM
51	Vimali	68	1391050	R	T3N1M0	6x4	2x1.5	IDC	C.T	MRM
52	Lakshmi	52	1406301	L	T4bN1M0	6.2x7.1	3.1x3.5	IDC	C.T	MRM
53	saradha	58	1390358	L	T4bN1M0	8.4x8.2	5.4x4.2	IDC	C.T	MRM
54	Muthulakshmi	63	1391638	L	T3N1M0	5x4.8	2.5x2.0	IDC	C.T	MRM
55	Andal	55	1391643	L	T4bN1M0	7x4	4x3	IDC	C.T	TM
56	Kasthri	52	1391582	R	T4bN1M0	9x7	5x4	IDC	C.T	-
57	Rajammal	54	1392857	R	T4bN1M0	10x7	6x4	IDC	C.T	-
58	Paiyanayaki	57	1397571	L	T3N0M0	6x5	3x2.1	IDC	C.T	MRM
59	Andal	63	1391643	L	T4bN2M0	8x9	4.5x6.0	IDC	C.T	-
60	Sakunthalal	58	1401080	R	T4bN2M0	9x9	5x6.5	IDC	C.T	-
61	Moomina devi	53	1406536	L	T3N1M0	6.6x4.5	2.3x2.3	IDC	C.T	MRM
62	Kamali	45	1407830	R	T4bN2M0	10x8	6x5	IDC	C.T	-
63	Saratha	53	1410618	R	T3N0M0	5x4	2x2	IDC	C.T	MRM
64	Vimala	51	1423428	L	T4bN2M0	9x6	5x4	IDC	C.T	TM
65	Chitra	53	1381027	L	T3N1M0	5x4	2.5x1.5	IDC	C.T	MRM

S.NO	NAME	Age Set	I.P.NO	SIDE	TNM STAGING	Tumour size before nact	Tumour size after NACT	HPE	U.S/C.T	Surgery
66	Kalyani	78	1387356	R	T4bN2M0	8x7	2x1.8	IDC	C.T	MRM
67	Kamatchi	44	1391236	L	T3N1M0	5x2	3x2.5	IDC	C.T	MRM
68	Kanaga	75	1403151	R	T3N1M0	7x3	2x1.5	IDC	C.T	MRM
69	Sathya	53	1412528	R	T3N1M0	3x4	3.1x3.5	IDC	C.T	MRM
70	uma	55	1420809	R	T4bN2M1	10x7	5.4x4.2	IDC	C.T	TM
71	Sathya bama	54	1393525	R	T4bN2M0	7.6x9	2.5x2.0	IDC	C.T	TM
72	Jothi	64	1395398	R	T4bN2M0	9.8x7.2	4.5x6.0	IDC	C.T	MRM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INTRODUCTION
LABC refers to a diverse and heterogonous group of peoples with breast cancer which represents one of the commonest malignancy of female population in our region.
Patients with this cancers include those with operablity at presentation, and inoperablity at presentation. Which include stage IIb, IIIa and IIIb. This study also included supra clavicular node in the locally advanced breast cancers.[1]
Over the past few decades, the management of the LABC has considerably evolved from radical mastectomy alone to multidisciplinary modalities involving surgery, chemotherapy and radiotherapy(RT) , with the advent of Neo adjuvant Chemotherapy many of the previously inoperable tumours become amenable to surgery.
Preoperative administration of hormonal therapy or systemic chemotherapy can result in considerable fall in tumour size in 50% to 80% of the LABC. Patients living with LABC have poor prognosis when treated with
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INTRODUCTION LABC refers to a diverse and heterogonous group of peoples with breast cancer which represents one of the commonest malignancy of female population in our region. Patients with this cancers include those with operablity at presentation, and inoperablity at presentation. Which include stage IIb, IIIa and IIIb. This study also included supra clavicular node in the locally advanced breast cancers. 1 Over the past few decades, the management of the LABC has considerably evolved from radical mastectomy alone to multidisciplinary modalities involving surgery, chemotherapy and radiotherapy(RT) , with the advent of Neo adjuvant Chemotherapy many of the previously inoperable tumours...